PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Kingsbury, Oliver CEC
Eli Lilly and Company
P.O. Box 6288
Indianapolis, IN 46206-6288
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.12.2005
Applicant's or agent's file reference X-16410 ✓	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/025593 ✓	25.08.2004 ✓	27.08.2003 ✓

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Sleex, C Tel. +49 89 2399-8044

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-16410	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/025593	International filing date *(day/month/year)* 25.08.2004	Priority date *(day/month/year)* 27.08.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/138, A61K31/40, A61K31/4025, A61K31/4375, A61K31/4462, A61K31/4468, A61K31/4525, A61K31/453, A61K31/4704, A61K31/4709, A61K31/5375, A61K31/5377, A61P25/00

Applicant
ELI LILLY AND COMPANY et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.07.2005	16.12.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Albrecht, S

Telephone No. +49 89 2399-7864

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/025593

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-282 as originally filed

   Claims, Numbers

   1-3 filed with telefax on 01.12.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 4
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/025593

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-3
Industrial applicability (IA)	Yes:	Claims	1-3
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/US2004/025593

Re Item I

Basis of the report

With his telefax of 01-12-05, the applicant has filed a new set of claims 1-3. These modifications do not introduce subject-matter which extends beyond the content of the original application, and thus fulfill the requirements of Art.34(2)(b) PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D7: ANONYMOUS: "Medication Reference" INTERNET ARTICLE, [Online] 2 August 2003 (2003-08-02), XP002305149 Retrieved from the Internet: URL:http://web.archive.org/web/20030802202920/http://www.patientcenters.com/autism/news/med_reference.html> [retrieved on 2004-11-11]

D12: WO02070457 A 12 September 2002

D13: EP0721777 A 17 July 1996

V.1. Novelty

Claims 1-3 appear to be novel over the available prior art, since none of the cited prior art documents disclose the use of atomoxetine or a compound of formula I as sole active agents for the treatment of the specific pervasive developmental disorders listed in claim 1.

V.2. Inventive step

V.2.1. Claim 1:

Claim 1 does not appear to involve an inventive step in the sense of Article 33(3) PCT, the reasons being as follows:

a) D12, which is considered to represent the most relevant state of the art, discloses the use of compounds of formula I or metabolic precursors thereof for the treatment of disorders linked to decreased neurotransmission of serotonin and/or norepinephrine in mammals, such disorders including i.a. autism (p.2, l.4-21; p.17, l.4-14). The metabolic precursor is preferably the selective norepinephrine reuptake inhibitor atomoxetine hydrochloride (p.1, l.11; p.15, l.7 - p.16, l.3; p.17, l.20-28).

b) The subject-matter of claim 1 differs from D12 in that D12 does not mention other pervasive developmental disorders, such as Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder and Pervasive Developmental Disorder not otherwise specified.

c) Nevertheless, it is known from D7 that selective norepinephrine reuptake inhibitors such as reboxetine are occasionally prescribed to people with autistic spectrum disorders (p.6, paragraphs 3 and 4). It may be argued that this disclosure does not provide a sufficiently strong incentive to the skilled person to select selective norepinephrine reuptake inhibitors in order to solve the technical problem of finding further means for the treatment of the pervasive developmental disorders listed in claim 1, in particular since D7 does neither explicitly recommend such use of reboxetine nor does it suggest its efficacy for this purpose. However, the skilled person being aware of the well-known fact that the symptomatology of autism and the other pervasive developmental disorders listed in claim 1 is very similar and that the differentiation of the different disorders can be quite problematic in clinical practice, would be prompted in light of the teaching of D12 taken alone or in combination with D7 to select norepinephrine reuptake inhibitors such as atomoxetine in order to treat further autistic spectrum disorders such as those listed in claim 1.

V.2.2. Claims 2, 3:

Dependent claims 2, 3 do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT with respect to inventive step. In particular, in view of the fact that the use of atomoxetine for the treatment of attention deficit/hyperactivity disorder is known in prior art (D13), it would be obvious for the skilled person to select the aforementioned compound for the treatment of patients in which attention deficit/hyperactivity disorder occurs comorbidly with a pervasive developmental disorder.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Kingsbury, Oliver CEC
Eli Lilly and Company
P.O. Box 6288
Indianapolis, IN 46206-6288
ETATS-UNIS D'AMERIQUE

RECEIVED
NOV 22 2005
ELI LILLY AND COMPANY
Patent Division

PCT

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 66)

	Date of mailing *(day/month/year)* 18 DEC 2005 / 18.11.2005
Applicant's or agent's file reference X-16410	**REPLY DUE** **within 1 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/025593	25.08.2004	27.08.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/138, A61K31/40, A61K31/4025, A61K31/4375, A61K31/4462, A61K31/4468, A61K31/4525, A61K31/453,

Applicant
ELI LILLY AND COMPANY et al.

1. ☒ The written opinion established by the International Searching Authority:
   ☒ is ☐ is not
   considered to be a written opinion of the International Preliminary Examining Authority

2. This second report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   Also: For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 27.12.2005

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Albrecht, S Telephone No. +49 89 2399-7864

Form PCT/IPEA/408 (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/US2004/025593

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this opinion is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

   Description, Pages

   1-282 as originally filed

   Claims, Numbers

   1-5 received on 11.07.2005 with letter of 07.07.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3,5
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations:

see separate sheet

Re Item I
Basis of the report

With his letter of 07-07-05, the applicant has filed a new set of claims 1-5. These modifications do not introduce subject-matter which extends beyond the content of the original application, and thus fulfill the requirements of Art.34(2)(b) PCT.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D12: WO02070457 A 12 September 2002
D13: EP0721777 A 17 July 1996

These documents were not cited in the international search report. Copies of the documents are appended hereto.

V.1. Novelty

V.1.1. Claims 1-3, 5 do not appear to be novel in the sense of Article 33(2) PCT, the reasons being as follows:

D12 discloses the use of compounds of formula I or metabolic precursors thereof for the treatment of disorders linked to decreased neurotransmission of serotonin and/or norepinephrine in mammals, such disorders including i.a. autism (p.2, l.4-21; p.17, l.4-14). The metabolic precursor is preferably atomoxetine hydrochloride (p.15, l.7 - p.16, l.3; p.17, l.20-28).

Hence, D12 anticipates the subject-matter of claims 1-3, 5.

V.1.2. Claim 4 appears to be novel over the available prior art.

V.2. Inventive step

V.2.1. Claims 1-3, 5:

Being not new, the subject-matter of present claims 1-3, 5 cannot be considered as inventive either.

V.2.2. Claim 4:

Dependent claim 4 does not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT with respect to inventive step. In particular, in view of the fact that the use of atomoxetine for the treatment of attention deficit/hyperactivity disorder is known in prior art (D13), it would be obvious for the skilled person to select the aforementioned compound for the treatment of patients in which attention deficit/hyperactivity disorder occurs comorbidly with autism.

VIA FACSIMILE

IN THE EUROPEAN PATENT OFFICE ACTING AS
PRELIMINARY EXAMINATION AUTHORITY UNDER THE PCT

Applicant Docket: X-16410
International Application No.: PCT/US2004/025593
Applicant: ELI LILLY AND COMPANY
Earliest Priority Date: 27 August 2003 (27.08.03)
International Filing Date: 25 August 2004 (25.08.04)
Invention Title: Treatment of Pervasive Developmental Disorders With Norepinephrine Reuptake Inhibitors

AMENDMENTS AND REMARKS
ACCOMPANYING REPLY TO SECOND WRITTEN OPINION

European Patent Office
D-80298
Munich, Germany

Attn: IPEA/EP

Dear Sir/Madam:

In response to the second Written Opinion dated 18 November 2005, the due for which is 18 December 2005, the following amendments and remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

In the Claims

Please replace page 283/1 of the application containing substitute claims 1-5, submitted on 7 July 2005, with substitute page 283/2 attached hereto, containing new claims 1-3.

REMARKS

Explanation of, and Support for, New Claims 1-3

Explanation

New claims 1-3 replace claims 1-5 as filed on 7 July 2005. New claims 1-3 differ from claims 1-5 filed 7 July 2005 in that new claim 1 incorporates the subject matter of claim 2, former claim 3 has been cancelled, and none of the presently submitted claims recites Autistic Disorder.

Support

Support for newly submitted claims 1-3 can be found, for example, in claims 1-5 submitted on 7 July 2005, and throughout the specification as originally filed.

As none of newly submitted claims 1-3 introduces any new matter into the application, entry thereof is believed to be in order, and is respectfully requested.

Item V: Novelty and Inventive Step

Novelty

As set forth in the Second Written Opinion dated 18 November 2005, claims 1-3 and 5 submitted 7 July 2005 are considered to lack novelty in view of the disclosure of D12. Claim 4 is considered to be novel over the available prior art.

Inventive Step

The Second Written Opinion also asserts that since claims 1-3 and 5 lack novelty, they cannot be considered inventive either.

Claim 4 is considered to lack inventive step in view of the combined disclosures of D12 and D13.

Applicant's Response

New claims 1-3 submitted herewith do not recite Autism or Autistic Disorder.

As D12 neither discloses nor suggests that either atomoxetine or 4-hydroxy atomoxetine can be used to treat a Pervasive Developmental Disorder selected from the group consisting of Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder, and

Pervasive Developmental Disorder Not Otherwise Specified either presenting alone or in combination with Attention-Deficit Hyperactivity Disorder as recited in the present claims, these claims are both novel and inventive compared to the disclosure of D12. Furthermore, D13 does not cure the deficiencies of D12 with respect to the treatment of the presently claimed indications as it only discloses the use of atomoxetine to treat Attention-Deficit Hyperactivity Disorder.

In view of the foregoing, Applicant respectfully submits that the present claims are both novel and inventive compared to the disclosures of D12 and D13, taken either alone or in combination. Applicant further respectfully submits that the present claims set forth inventions that are novel, inventive, and industrially applicable, and which are therefore deserving of patent protection. Withdrawal of all the objections set forth in the Second Written Opinion of the Searching Authority is requested, as is issuance by the Examiner of a favorable International Preliminary Examination Report.

Unless otherwise expressed herein, Applicant disagrees with any statement in the Second Written Opinion to the effect that the invention as disclosed and claimed in the present application fails to possess novelty, inventive step, or industrial applicability, or that it is not useful or is obvious. Any arguments or amendments submitted herewith are for the purpose of obtaining a preliminary and non-binding opinion under the provisions of PCT Article 33, and should be considered without prejudice to any arguments or amendments which may be advanced in the national or regional phase examination of this application.

Applicant requests the opportunity for an interview in the event that, after consideration of the foregoing arguments, the Examiner intends to issue an IPER that is not entirely positive.

Respectfully submitted,

Charles E. Cohen

Charles E. Cohen, Ph.D.
Attorney for Applicant
Phone: 317-433-4983 (USA)

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

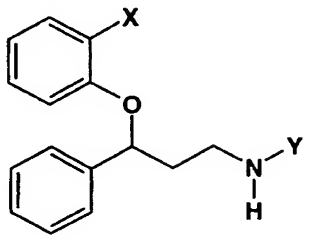
01 December 2005

Attachment:

1. Substitute sheet containing new claims 1-3 (page 283/2)

We Claim:

1. Use of a norepinephrine reuptake inhibitor selected from the group consisting of atomoxetine and a compound of formula I:



wherein X is C_1-C_4 alkylthio, and Y is C_1-C_2 alkyl, or

a pharmaceutically acceptable salt thereof,

as sole active agent for the manufacture of a medicament for the treatment of a Pervasive Developmental Disorder selected from the group consisting of Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified.

2. The use of claim 1, wherein Attention-Deficit Hyperactivity Disorder occurs comorbidly with said Pervasive Developmental Disorder.

3. The use of claim 1 or 2, wherein said norepinephrine reuptake inhibitor is atomoxetine hydrochloride.